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REVIEWS

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Capillary leak and endothelial permeability in critically ill patients: a current overview

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Abstract

Capillary leak syndrome (CLS) represents a phenotype of increased fluid extravasation, resulting in intravascular hypovolemia, extravascular edema formation and ultimately hypoperfusion. While endothelial permeability is an evolutionary preserved physiological process needed to sustain life, excessive fluid leak—often caused by systemic inflammation—can have detrimental effects on patients' outcomes. This article delves into the current understanding of CLS pathophysiology, diagnosis and potential treatments. Systemic inflammation leading to a compromise of endothelial cell interactions through various signaling cues (e.g., the angiopoietin–Tie2 pathway), and shedding of the glycocalyx collectively contribute to the manifestation of CLS. Capillary permeability subsequently leads to the seepage of protein-rich fluid into the interstitial space. Recent insights into the importance of the sub-glycocalyx space and preserving lymphatic flow are highlighted for an in-depth understanding. While no established diagnostic criteria exist and CLS is frequently diagnosed by clinical characteristics only, we highlight more objective serological and (non)-invasive measurements that hint towards a CLS phenotype. While currently available treatment options are limited, we further review understanding of fluid resuscitation and experimental approaches to target endothelial permeability. Despite the improved understanding of CLS pathophysiology, efforts are needed to develop uniform diagnostic criteria, associate clinical consequences to these criteria, and delineate treatment options.

Keywords Capillary leak syndrome, Critical care, Fluid balance, Endothelial permeability, Angiopoietin-2

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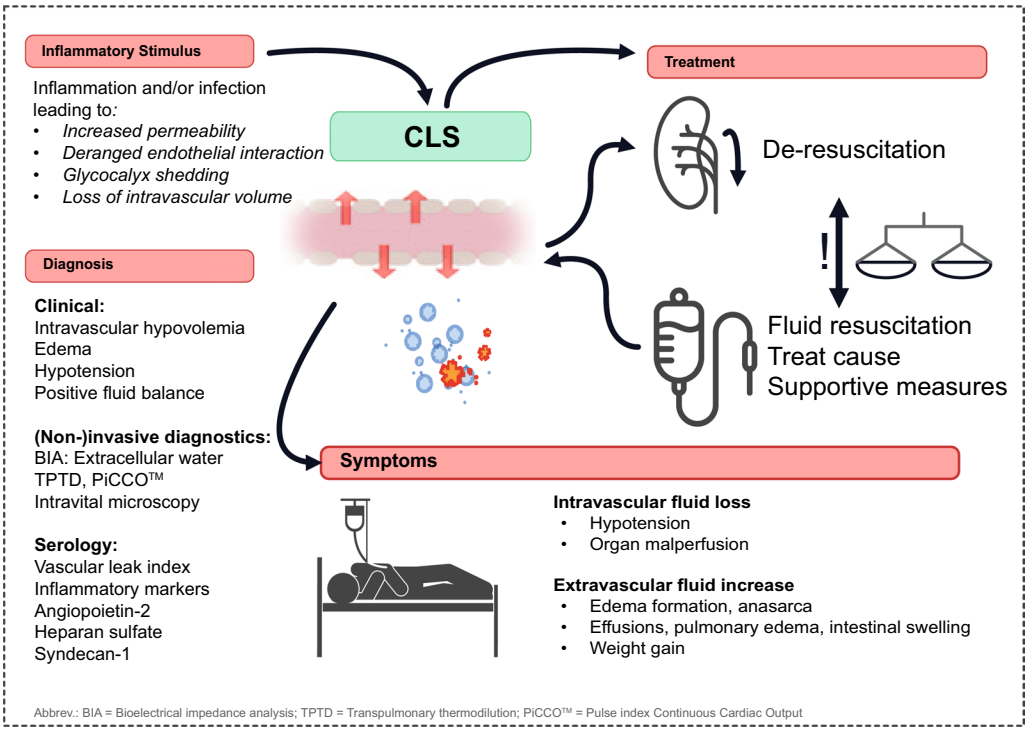
Graphical Abstract



Introduction

Capillary leak syndrome (CLS) refers to a syndrome of deranged fluid homeostasis, often observed in critically ill [1–3]. In clinical practice, CLS is frequently defined by excessive fluid shift from the intravascular to the extravascular space, resulting in intravascular hypovolemia, extravascular edema formation, and hypoperfusion—necessitating further fluid resuscitation [3].

In health, fluid exchange between intravascular and extravascular spaces is vital for maintaining the body's homeostasis. However, disturbances in this delicate equilibrium, often driven by systemic inflammation (e.g., sepsis) can lead to the clinical picture of CLS [4–6].

Despite efforts to define CLS, there is no established clinical definition nor accepted diagnostic criteria [1, 3]. Previously, Marx et al. characterized CLS as a fluid extravasation, resulting in edema and hypoperfusion [3]. The authors studied septic shock patients using various methods such as indocyanine green measurements, chromium-51 labeled erythrocytes, and colloid osmotic pressure measurements, aiming to differentiate CLS from other hypo-oncotic conditions and clinical scenarios associated with fluid retention [3]. The definition of CLS proposed by Marx et al. in 2000 emphasized three main aspects: intravascular hypovolemia despite fluid resuscitation, generalized edema, and hemodynamic instability. This pivotal description, while not universally adopted, offers valuable insight into the key features of CLS, aiding in the differentiation of this syndrome from other conditions that share similar clinical manifestations. It underlines the necessity for an accepted definition of this syndrome to develop targeted and effective therapeutic interventions [3].

This article will review the current understanding adding new aspects of CLS in clinical practice, and give an overview about the pathophysiology, clinical presentation, diagnostic and therapeutic options.

Pathophysiology of CLS and implications

Triggers and key features

A CLS phenotype can be triggered by numerous disease states as well as certain medications and toxins [7]. Depending on the literature source, terms like "generalized hyperpermeability syndrome", "endothelial permeability" or "capillary leakage" may be used synonymously for CLS. As an important semantic distinction, the "idiopathic systemic capillary leak syndrome", also referred as Clarkson's disease [8], needs to

be distinguished from CLS observed in the critically ill with a clear triggering condition. Clarkson's disease is a rare and potentially fatal condition that is characterized by recurrent episodes of highly acute fluid shifts in otherwise healthy individuals, which can occur in two phases: an initial phase of fluid extravasation associated with syncope, dyspnea, and hypovolemia, followed by a second phase characterized by fluid reabsorption with polyuria and flash pulmonary edema [9]. This condition is rare with limited case reports describing these patients, however the term "systemic capillary leak syndrome" has the potential to cause confusion and impede accurate scientific exchange.

Aside from sepsis triggering CLS [6], other inflammatory states like cardiac surgery using cardiopulmonary bypass [10], anaphylaxis, or major burn injuries can lead to a CLS phenotype. Other rare causes have been described and span from ovarian hyperstimulation syndrome [11, 12], hemophagocytic lymphohistiocytosis [13, 14], viral hemorrhagic fevers [15, 16], autoimmune diseases [17–19], snakebite envenomation [20, 21], and ricin poisoning [22]. Certain drugs, including some interleukins (ILs) [23], monoclonal antibodies and gemcitabine [24], anti-thymocyte globulin may also hold the potential to induce a CLS phenotype [7]. Despite the diverse terminology and triggering factors, the core manifestations remain intravascular hypovolemia, generalized edema, and hemodynamic instability, forming the cornerstone of any definition for this clinical entity.

Due to the heterogenous clinical definition, the relevance of CLS is hard to accurately depict in clinical practice. Good scientific evidence for CLS' impact on general patient outcomes is lacking. However, its pathophysiological effects on fluid distribution and oxygen transfer can be delineated from a pathophysiological standpoint. Given that endothelial hyperpermeability is a key part of the host's response to infections, some authors hypothesize that CLS could be a putative target for novel sepsis treatment [25]. A key feature of CLS is represented by capillary permeability, which results in fluid shifts and a decrease in colloid oncotic pressure, often exacerbated by the subsequent fluid resuscitation [26, 27].

Furthermore, an important pathophysiological consideration is the potentially harmful effect on the microcirculation, the network of small vessels crucial for oxygen delivery to the tissues. When fluid leaks out of these vessels into the surrounding tissue, it increases the diffusion distances between capillaries and cells [28]. The systemic implications of CLS underscore the importance of strategies to mitigate the detrimental effects of fluid shifts in key organ systems, maintaining intravascular euvolemia, and ensure adequate oxygenation at the tissue level.

Inflammatory breakdown of endothelial barrier

Physiologic vascular permeability is a tightly controlled process that is vital to the overall bodily function. However, the extent of permeability varies not only in health and disease, but is also specific to different organ systems and metabolic needs, thereby mirroring each organ's unique biological requirements.

The endothelium is a single layer of cells lining the interior surface of all blood vessels. Its surface area has been estimated to be equivalent to a soccer field [29, 30]. Various endothelial subtypes have been described (e.g., fenestrated, non-fenestrated, sinusoidal), fulfilling specialized and organ-specific functions. It plays an integral role in a diverse array of vascular functions, creating a complex interface between the extra- and intravascular space. Endothelial cells intricately regulate permeability across the endothelium. This is largely due to their ability to form tight, adherens, and gap junctions, the latter of which allow for the exchange of ions, various metabolites, and regulatory factors [31]. Such dynamic functionality marks endothelial activation as a key hallmark for capillary leak [30]. Furthermore, the vascular endothelium acts as a semipermeable barrier, controlling the exchange of macromolecules and fluids between interstitial fluid and blood. Vascular leakage can occur through two primary pathways [32]: the paracellular and the transcellular pathway [33].

The function of the endothelial barrier varies across different segments of the microvasculature, with permeability increasing from arterioles to venules [34]. There are three types of capillaries: continuous, fenestrated, and discontinuous, which display functional differences specific to the organ [35]. While fenestrated capillaries feature openings with a diameter of 60 nm, their permeability is primarily restricted to water and minor hydrophilic solutes. This limitation is due to the presence of a diaphragm that only allows molecules smaller than 5 nm to pass through [31, 36]. Venules, in contrast, possess endothelial cells with greater permeability characteristics, allowing not just fluids but also solutes and proteins to pass. These cells are particularly responsive to agents that increase permeability [31]. Another factor contributing to the heterogeneity of endothelial permeability across various vascular beds is the extent of coverage by supporting cells, such as pericytes [37]. In the context of inflammation, leukocytes typically exit the bloodstream through venules. This is facilitated by endothelial cells that, when exposed to inflammatory cytokines, present adhesion molecules to which leukocytes can attach. Large veins, however, are less prone to fluid leakage and are not as responsive to agents that increase permeability [38].

In inflammation, the endothelial barrier can be compromised in its integrity (see Fig. 1) [39]. During conditions such as infection (via pathogen-associated molecular patterns, PAMPs) or tissue injury (via damage-associated molecular patterns, DAMPs), endothelial cells undergo a transformation into an activated, proinflammatory state [39]. This activated state is typified by the production and release of various proteins stored in intracellular vesicles known as Weibel–Palade bodies [40]. When endothelial cells are activated, they release proteins such as tissue factor, P-selectin, von Willebrand factor, interleukins, angiopoietin-2 (Ang-2) and many more into the bloodstream [41]. Furthermore, stimulated endothelial cells can produce and distribute proinflammatory cytokines into the bloodstream, which amplifies and exacerbates the inflammatory reaction. In a physiological state, this aims to attract immune cells to localized sites of infection or damage [40]. In case of systemic activation, it may lead to deleterious consequences. Endothelial cells further produce chemoattractants and adhesion molecules, thereby promoting the movement of leukocytes towards inflamed tissues [42, 43]. In a localized inflammatory process, the increase in vascular leakage supports the process of blood cell trafficking and the extravasation of macromolecules to the site. On the local level, this response is beneficial for resolving inflammation and facilitating tissue repair at a given site of an infection [44, 45]. However, when the proinflammatory response escalates to a systemic level, it can lead to a widespread compromise of the endothelial barrier function. This may lead to CLS with relevant fluid shifts, hypotension, intravascular hypovolemia with the need for fluid resuscitation and edema formation. Of note, Kubicki et al. were able to show that CLS in consequence to pediatric cardiac surgery with cardiopulmonary bypass is associated with tissue inflammation as quantified by microdialysis [46]. In case of ongoing hypoperfusion, severe consequences such as organ dysfunction are possible (e.g., acute respiratory distress syndrome, acute kidney injury, etc.) [39, 47, 48]. Furthermore, little is known about the resolution from endothelial dysfunction when inflammatory triggers subside, thus prompting future investigations.

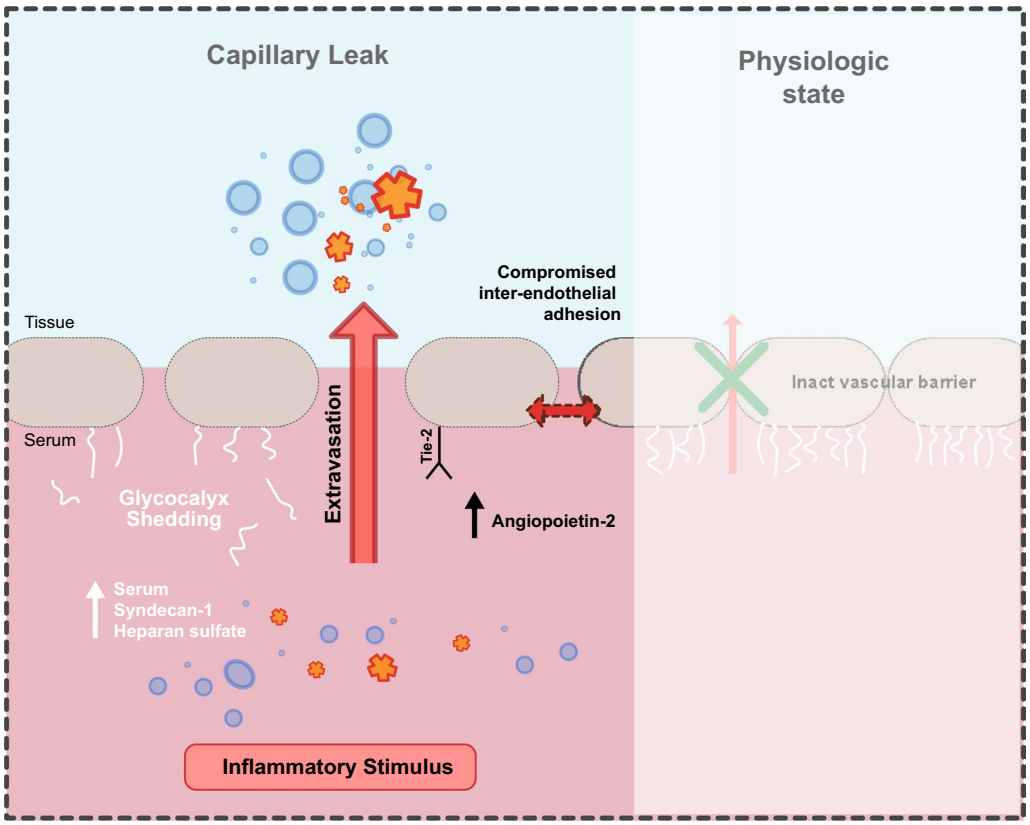


Fig. 1 Pathophysiological understanding of selected features of capillary leak including inflammation-induced glycocalyx shedding with increased circulation serum glycocalyx markers (syndecan-1, heparan sulfate), as well as angiopoietin-2/Tie2 signaling leading to compromised inter-endothelial adhesion

Pathways in maintaining and compromise of inter-endothelial adhesion

Recent studies have shed light into mechanisms that are involved in destabilizing the endothelial barrier function, prompting the need for innovative therapeutic strategies targeting these pathways to enhance patient outcomes [39]. One identified pathway central to regulation of inter-endothelial adhesions and vascular permeability is the angiopoietin–Tie2 signaling axis [39, 41, 49, 50]. This pathway involves the Tie2 receptor, a second class tyrosine kinase that is almost exclusively expressed by endothelial cells, and its associated ligands, namely angiopoietin 1 (Ang-1) and Ang-2 [39].

Under normal physiological conditions, Tie2 is significantly activated, thereby inhibiting the transcription factor Foxo1, which is responsible for transcribing the Ang-2 gene [51]. However, during inflammation, Ang-2 antagonizes Tie2, disrupting this inhibitory process and permitting Foxo1 to produce more Ang-2 [52]. The activation of Tie2 during vascular quiescence triggers a signaling cascade that strengthens the endothelial cytoskeleton via the inhibition of small GTPases such as RhoA [38, 53]. Nevertheless, this safeguarding effect is negated during inflammation due to the inhibition of Tie2 induced by Ang-2, which results in the production of adhesion molecules and facilitates the migration of immune cells into the inflamed tissue [39, 54]. Another layer of complexity has recently been added to this concept, as it has been observed that not just the activation but also the expression of Tie2 can be severely altered during systemic inflammation [55]. Mechanistically, this could be addressed as a proteolytic shedding process of the Tie2 ectodomain by matrix metalloproteinase 14 [56, 57].

In a resting state, mesenchymal cells, mostly pericytes, secrete Ang-1, which acts as a stimulant for the Tie2 via its phosphorylation, thereby promoting the survival of endothelial cells and maintaining the stability of blood vessels with augmenting its inter-endothelial cellular adhesions [58, 59]. Conversely, Ang-2, stored within the endothelial Weibel–Palade bodies, acts as a context-dependent inhibitor to the Ang1–Tie2 interaction, effectively reducing the activation of the Tie2 receptor [60, 61]. When inflammatory cytokines stimulate the endothelial cells, Ang-2 is released from its storage within the cells, leading to an autocrine deactivation of the Tie2 receptor, a process further intensified by the shedding of the Tie1 ectodomain [62]. It has been observed that Ang-2 levels rise sharply within hours of the onset of sepsis in patients, and these elevated levels have been linked to adverse outcomes and increased mortality rates [63, 64].

It is worth noting that the interplay of these mechanisms result in a reinforcing cycle of inflammation [39]. Besides sepsis, an imbalance in angiopoietin has been associated with negative outcomes in a range of conditions, such as hantavirus, dengue virus, influenza, malaria, and sterile inflammation resulting from extensive surgeries and/or trauma [65–70]. This underscores the potential of the Ang/Tie2 axis as a therapeutic target in various systemic inflammation conditions. Further research into the modulation of this critical pathway may open doors to new therapeutic strategies for systemic inflammation.

Syndecans, comprising Syndecan-1 to -4, are transmembrane proteoglycans essential in endothelial barrier integrity, especially under inflammatory conditions [71]. These proteoglycans interact with various ligands, influencing cell adhesion, angiogenesis, and inflammation [72]. Syndecan-1 and -4 are particularly noteworthy, regulating inflammatory responses in contexts like myocardial injury and sepsis [71, 73]. Syndecan-2 responds to inflammatory stimuli in several cell types, further emphasizing the syndecans' role in inflammation [74, 75]. Syndecan-1 and -4 are pivotal in leukocyte extravasation, facilitating initial rolling and then modulating adhesion and migration to balance inflammation [76–78]. Syndecan-1 also controls leukocyte adhesion to the endothelium, crucial for inflammation regulation [71, 79]. Syndecan-3, while less studied compared to its counterparts, has shown involvement in endothelial function across various vascular beds and influences angiogenesis and vascular permeability [80–83]. In conclusion, current evidence underscores the multifaceted roles of syndecans in endothelial dynamics, particularly emphasizing their significant contribution to inflammation regulation and vascular response under various pathological conditions.

Glycocalyx shedding

The endothelial glycocalyx (eGC), a coating of sugar molecules on the inner surface of the vascular endothelium, is vital for maintaining vascular stability, fluid homeostasis, and serves as a sophisticated protective shield against inflammation and coagulation [84]. This highly dynamic molecular shield is now viewed as a pivotal player in the pathophysiology of sepsis [85] and has been shown to be compromised in various surgical procedures [10].

In the course of sepsis, the degradation of the glycocalyx takes place through two interrelated "sheddase" mechanisms [85]. These mechanisms pertain to the breakdown of glycosaminoglycans and the cleavage of the core proteoglycans [86–88]. Studies have identified circulating glycosaminoglycans and proteoglycans extracellular domains in sepsis, indicating that these components are released from the glycocalyx, thereby contributing to its thinning and degradation [89–92]. One of the key players in this degradation process is an enzyme known

as heparanase-1 [89–92], the only identified mammalian enzyme capable of degrading heparan sulfate polysaccharides into shorter chain oligosaccharides [93]. Heparanase-1 is activated during sepsis, contributing significantly to the degradation of the glycocalyx [85]. The role of heparan sulfate degradation in sepsis, mediated by heparanase-1, has been solidified through numerous preclinical and clinical studies [85, 89–92]. At the same time, septic patients acquire a relevant deficiency of the endogenous heparanase-1 counterpart termed heparanase-2. This dys-equilibrium may represent a novel therapeutic target [94, 95].

Another critical element of the glycocalyx is hyaluronan. Uniquely, hyaluronan is unsulfated and not covalently bound to proteoglycans [96, 97]. Despite its structural differences, hyaluronan plays a crucial role in maintaining the structural stability of the glycocalyx, primarily through its ability to form complexes with proteins and other sulfated glycosaminoglycans [98]. In sepsis, patients have been observed to possess elevated levels of serum hyaluronan, indicating an increase in its degradation [99, 100]. The exact mechanism of hyaluronan degradation in sepsis, however, remains unclear, and this is an active area of research. While there is less understanding regarding the behavior of chondroitin sulfate, dermatan sulfate, and keratan sulfate during sepsis, it is hypothesized that proteoglycans carrying these glycosaminoglycans are expelled from the endothelial glycocalyx during this severe condition [87, 100, 101]. However, the exact mechanism of this shedding process and the identification of the enzymes involved remain as open questions in the field. Further complicating the process, the ectodomains of proteoglycans are also discharged from the endothelial glycocalyx during sepsis [102–104]. This is largely mediated by a group of enzymes known as matrix metalloproteinases (MMPs) and members of the A Disintegrin and Metalloproteinase (ADAMs) family. These enzymes are capable of cleaving proteoglycans from the endothelial glycocalyx and their plasma concentrations are correlated with the severity of sepsis [105–107].

The activation of these sheddase mechanisms is not random. Instead, it is modulated by upstream factors, including proinflammatory cytokines [85]. For instance, sepsis-related activation of the glycosaminoglycans sheddase heparanase-1 is dependent upon endothelial-derived TNF-α [89]. Furthermore, the Ang-2/Tie2 pathway, critical in maintaining endothelial homeostasis, has been shown to regulate glycocalyx sheddases [87, 108–110]. Interestingly, other molecules such as macrophage migratory inhibitor factor, phorbol esters, and tissue inhibitors of matrix metalloproteinases, which are involved in glycocalyx degradation in other diseases, may also be relevant to septic glycocalyx degradation [111–116].

The destructive process of glycocalyx during sepsis has substantial physiological implications. The loss of this protective barrier directly impacts local tissue, but the degradation products themselves can also circulate and affect distant sites in the body [85]. This leads to a system-wide impact that contributes to fluid shifts and the multiple organ dysfunction often seen in septic patients. The extent and the specific mechanisms through which glycocalyx degradation affects the progression and prognosis of sepsis are still being uncovered. This understanding is critical for the development of therapeutic strategies to preserve the eGC, attenuate the inflammatory response, and ultimately improve the outcomes of sepsis.

Fluid overload and dynamics

The human body contains various fluid compartments, both intravascular and extravascular, which have specific volumes and protein contents. According to indicator dilution studies, a healthy 70 kg adult typically has about 3 L of plasma, containing around 210 g of protein [117]. On the other hand, the same adult will have approximately 12 L of interstitial fluid. This fluid resides in a gel phase and contains 240–360 g of protein. The capillary pressure in this system is higher than the pressure in the interstitial space, which drives the movement of the solvent and its small lipophobic solutes towards the interstitial space [118]. Trans-endothelial fluid shifts are regulated by the vascular barrier in addition to hydrostatic and oncotic forces, as described by the revised Starling equation [119]. In healthy organs, the increased permeability and movement of proteins and plasma fluid are temporary and decrease once the stimulating factor is removed. Edema is traditionally perceived as a consequence of a pressure-driven net outward filtration in the capillary, partially reversed by fluid reabsorption at the venous end by an oncotic pressure gradient [120]. Contrary to traditional perspectives, more recent theories propose that continuous net filtration is the norm in most capillary networks [121]. Apart from an increased pressure gradient, edema can also be caused by hypo-oncotic states, changes in permeability and impaired lympathics.

The capillary wall includes a glycocalyx layer, which is a complex meshwork of glycosaminoglycans and additional glycoproteins. This layer serves as a filtration barrier, featuring gaps where capillary filtration takes place [121–123]. The movement occurs through regulation of the glycocalyx and the occasional breaks in the inter-endothelial junctions. These breaks constitute less than 0.1% of the total endothelial surface area, allowing a highly regulated fluid exchange process [117]. The

glycocalyx layer was previously assumed to have an almost perfect reflection coefficient for proteins, particularly albumin. However, albumin diffusion through capillary pores results in about half of the body's albumin content residing extravascularly, with interstitial oncotic pressure reaching 30–60% of plasma oncotic pressure [124]. The complexity of the interstitial space has been underestimated in the past. It actually consists of a triphasic system that includes freely moving fluids, a gel-like phase rich in large polyanionic glycosaminoglycans molecules, and a collagen framework [117, 124]. Albumin is predominantly absent from this luminal surface, leading to a stronger intravascular oncotic pressure than what direct measurements of interstitial albumin concentration would suggest [125]. As a result, the net filtration process is more influenced by the oncotic pressure beneath the endothelial glycocalyx than by the capillary membrane itself [123].

The clinical consequences of these fluid shifts can be manifold, yet not immediately visible to the clinician. The lungs are especially prone to pulmonary edema due to the unfavorable ratio of endothelium per tissue with the clinical potential to impact gas exchange, and predispose the lungs to further infectious complications [126]. Additionally, the gastrointestinal tract may become edematous, leading to paralytic ileus, an increase in intra-abdominal pressure and subsequent tissue hypoxia, and impaired wound healing [127, 128]. It is noteworthy that the endothelium is highly heterogeneous across different vascular beds; for example, CLS commonly affects various organs but is rarely observed in the brain due to the unique properties of the blood–brain barrier, including a higher pericyte-to-endothelial cell ratio that contributes to its greater impermeability [129].

While CLS is widely acknowledged in the critical care settings, there is a surprising lack of clinical studies exploring its impact on organ dysfunction and mortality [1]. This may stem from the current absence of accepted diagnostic criteria for CLS. However, associated conditions like an inflammatory state and positive fluid balance—circumstances inevitably related to CLS—correlate with higher mortality rates in the ICU [130]. For example, elevated levels of serum cytokines are commonly observed in non-survivors of critically illness, and a positive fluid balance is acknowledged as an independent predictor of outcomes in patients with sepsis [131, 132].

Fluid management can be complex in ICU settings, demanding a thorough understanding of body fluid homeostasis [133]. Fluid overload, which comprises whole body water, i.e., extra- and intravascular fluid, can be detrimental and associated with negative outcomes in patients who are critically ill [134–145]. It has been linked to extended duration of mechanical ventilation [135], increased rate of AKI [136] and renal replacement therapy (RRT) [137], longer ICU stays [135], and increased risk of infectious complications [141]. Furthermore, fluid overload can precipitate intra-abdominal hypertension in ICU patients, regardless of the underlying reason for their admission [142]. In all the aforementioned patient categories, fluid overload is consistently associated with increased mortality rates [134, 137, 138, 140–145]. A systematic review by Messmer et al. in 2020, which encompassed 31 observational and three randomized controlled trials involving a total of 31,076 ICU patients, confirmed a significant correlation between fluid overload and cumulative fluid balance with mortality [146].

While there is a lack of direct evidence on CLS and its impact on patient outcomes, the documented adverse outcomes related to fluid overload strongly underline the importance of further exploring excessive endothelial permeability in the ICU settings. Future research in this area could profoundly influence management strategies and potentially improve outcomes for critically ill patients. Therapeutically, IV fluids may only exert a transient effect on hemodynamics due to their half-life and physiological features to rather liberally cross the vascular barrier [147–149]. It is estimated that less than 5% of infused crystalloid may remain in the vasculature after 1 h [150].

The presence of hypovolemia with peripheral edema represents a counterintuitive scenario that has often baffled physicians. Fluids in the intercellular space can be categorized into two types: unbound fluid and fluid that is part of the gel phase. The gel phase consists of a lattice-like structure made up of collagen and various other fibrous matrix proteins [151]. Fluids are typically free to move between the interstitial space and plasma. Post-filtration, these fluids are channeled back into the circulatory system through the lymphatic network. However, pathological states and certain drugs can disrupt this equilibrium [151]. In inflammatory conditions like sepsis, the fluid's return from the interstitial space towards the plasma may be significantly hindered, leading to the characteristic triad of low blood volume, low albumin levels, and peripheral edema [151, 152]. Even general anesthesia, without the use of mechanical ventilation, has been observed to cause an accumulation of crystalloid fluid, that was previously infused, in a slowly equalizing segment of extravascular spaces [151, 153]. To comprehend the fluid kinetics, it is necessary to integrate data from various fields, including interstitial fluid physiology, lymphatic pathology, and inflammation. It is crucial to understand that the electrolyte composition of the majority crystalloids does not significantly affect kinetics

of fluids and, consequently, has limited effects on interstitial fluid pressure [154].

Diagnostic approach

Clinical diagnosis

Diagnosis of CLS is complex (see Fig. 2). So far, no established diagnostic criteria for CLS exist. The need for fluid resuscitation is a critical aspect of CLS diagnosis and management. Clinical hallmarks of CLS may encompass hemodynamic instability, intravascular hypovolemia and generalized edema [7]. Most evident to the clinician at bedside is the systemic pitting edema—but especially effusions in the thoracic and abdominal cavities, non-cardiogenic pulmonary edema, and intestinal swelling can contribute to worse outcomes [155]. While the diagnosis of CLS itself remains a complex endeavor, the assessment of edema, a hallmark feature, presents its own set of challenges. Though various methods for the quantification of peripheral edema exist—ranging from clinical assessments to ultrasound and other advanced imaging modalities—there are no standardized guidelines for the critical care setting [156, 157]. The most common method remains a subjective pitting test, where the severity of edema is graded based on pit depth and skin recovery time [157]. This traditional approach, although quick and widely used, lacks the objectivity and reliability needed for critical assessment.

The management of fluid balance in critically ill patients is a nuanced task. Excessive fluid resuscitation can lead to hypervolemia, ultimately increasing the damage to the glycocalyx and increased vascular permeability [130, 142]. On the other hand, hypovolemia is detrimental for organ perfusion. The diagnosis of CLS can be challenging given the lack of standardized criteria and the varied clinical presentations [1, 3]. Yet, a careful and comprehensive evaluation of patient status, considering the clinical context and use of appropriate diagnostic tools, which will be described below, can assist in identifying the CLS phenotype [1].

Non-invasive evaluation of extracellular water

Bioelectrical impedance analysis (BIA) offers an approach for non-invasively quantifying the water contents inside and outside cells [158, 159]. This method measures impedance due to the varying electrical conductivity of different biological tissues such as muscle and fat. Given that electrical conductivity correlates with electrolyte and/or water content, BIA can provide a quantitative evaluation of the body's water content, along with fat and muscle mass [159–162].

In a previous study by Marx et al. in critically ill patients, the extracellular water, derived using BIA, correlated well with invasive measurements of extracellular water content [3]. Patients with an elevated extracellular

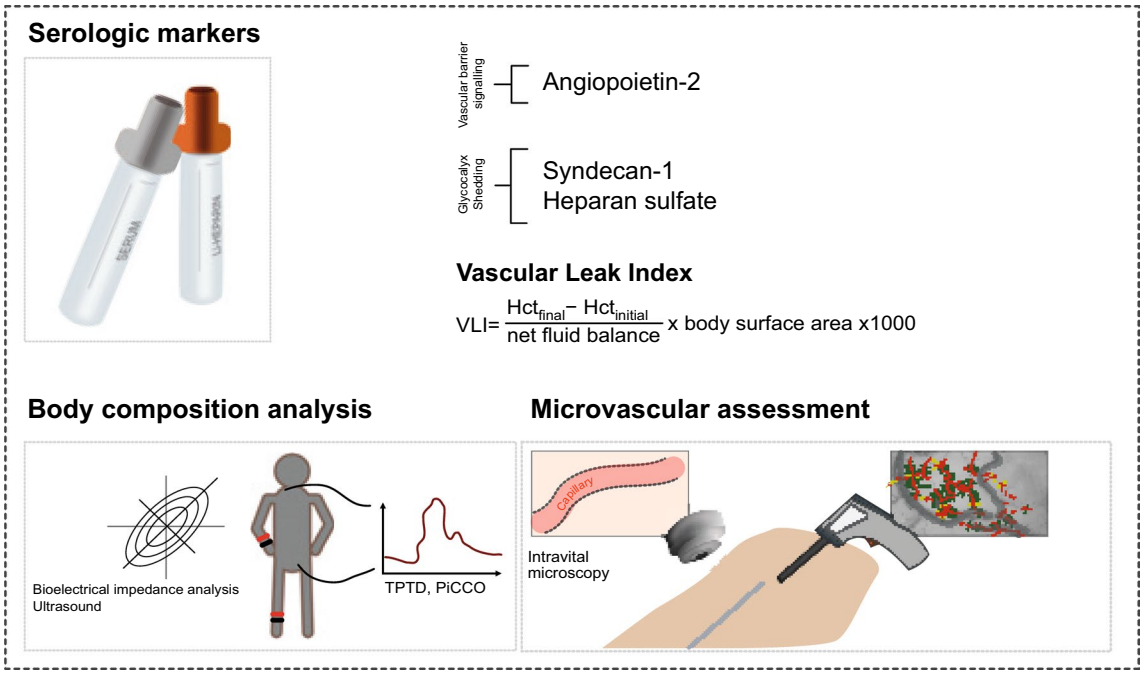


Fig. 2 Diagnostic approach to capillary leak syndrome (CLS): both serological markers related to glycocalyx shedding and vascular barrier signaling, as well as the vascular leak index can hint towards a CLS phenotype. More nuanced diagnostic approaches comprise bioelectrical impedance analysis (BIA), transpulmonary thermodilution (TPTD), PiCCO™ (pulse index continuous cardiac output), and intravital microscopy

water ratio on the third day in the ICU showed a higher likelihood of postoperative complications and in-hospital mortality [159]. In a recent study conducted on patients undergoing multivisceral debulking surgery, thoracic fluid content, assessed via electrical cardiometry, was found to continuously increase up to the third postoperative day and remained elevated until discharge [163]. This prolonged alteration in fluid status suggests that bioelectrical impedance analysis, including metrics like thoracic fluid content, may offer nuanced insights into volume shifts and their association with postoperative complications. Hence, this non-invasive measurement can be an effective tool for managing volume status, tailoring further therapy, and improving the prognosis for patients in the ICU.

Serum markers and CLS-scoring system

In their prospective study, Wollborn et al. sought to find common characteristics of CLS in a heterogenous cohort of critically ill patients [1]. They employed a variety of measurement techniques, from non-invasive BIA to serum biomarker analysis, to distinguish patients with CLS from those without [1]. The findings indicated that specific biomarkers previously identified in CLS pathophysiology, particularly Ang-2, showed significantly higher concentrations in CLS patients [1]. Other markers of endothelial integrity, such as the inter-endothelial adherens junction molecule VE-cadherin, and glycocalyx markers like syndecan-1 were elevated in CLS patients as well. In their statistical modellings, Wollborn and colleagues derived a scoring system ("CLS-Score") which involved seven parameters: ultrasound echogenicity to determine the degree of edema, the Sepsis-related organ failure assessment score (SOFA) score for disease severity, Ang-2, syndecan-1, ICAM-1, lactate, and the proinflammatory cytokine interleukin-6 [1]. By incorporating these components, the score aimed to provide a more objective diagnostic tool for CLS. Many of the identified hallmarks were recently reproduced in a study in cardiac surgery patients [10].

Vascular Leak Index

As a straightforward yet effective approach to gauge vascular leak in patients suffering from sepsis, Chandra et al. developed the Vascular Leak Index in 2022 [164]. The Vascular Leak Index is calculated using a formula which considers the change in the hematocrit levels at two different timepoints during fluid administration, and the net volume of the administered fluid [164]. In essence, the Vascular Leak Index shows the correlation between the quantity of fluid infused and the change in hematocrit, thereby providing an indication of the amount of fluid that remains in or has escaped from the vascular space. This correlation is normalized to account for differences in each patient's blood volume. The result is then multiplied by 1000 for easier interpretation. By using large ICU databases, the researchers' analysis revealed that higher Vascular Leak Index values are linked to an increased risk of in-hospital death. Furthermore, patients with high Vascular Leak Index values may be at a greater risk of fluid accumulation [164]. A possible limitation is that the Vascular Leak Index cannot differentiate between effects of vascular leak versus concurrent vasodilation or vasoconstriction, especially on the venous side leading to an increase or decrease of venous volume and thereby changing the hematocrit, too [165].

Invasive assessment of fluid status

Among more invasive diagnostic tools, the use of transpulmonary thermodilution not only presents an approach for hemodynamic monitoring, but also to approximate a patient's fluid status [166]. Extravascular lung water is defined as the fluid volume outside the pulmonary vasculature, within the interstitial and alveolar spaces [166, 167]. It was previously validated against the reference method of gravimetry in autopsy studies [167–169]. Transpulmonary thermodilution (e.g., with use of the PiCCO™ system) and can be helpful in bedside clinical diagnosis and decision-making. It has been observed that an elevated extravascular lung water is linked to a higher mortality risk in ICU patients [166]. This association held true for both acute respiratory distress syndrome patients and critically ill patients without acute respiratory distress syndrome, suggesting the broad applicability of extravascular lung water as an indicator of disease severity [166]. It is important to clarify that extravascular lung water is a measure of accumulated extravascular water and not a direct indicator of permeability. The Pulmonary Vascular Permeability Index can further distinguish whether the elevated extravascular lung water may be due increased permeability (high Pulmonary Vascular Permeability Index) [170]. It has to be noted that lung-specific pathologies can lead to an increase in extravascular lung water due to localized increase in permeability which may not necessarily represent systemic vascular leak.

Monitoring endothelial damage and microcirculation

Intravital microscopy utilizing sidestream darkfield or incidental darkfield imaging is gaining popularity for the assessment of the sublingual microcirculation, a non-invasive method that visualizes red blood cells within the microvasculature with light emitted by a light-emitting diode probe, which is then reflected by hemoglobin and detected by a special camera [171]. This technique facilitates the estimation of total vessel density, perfused

vessel density, proportion of perfused vessels, and the microvascular flow index, typically through offline computer analysis [172–175].

Moreover, the intravital microscopy imaging of red blood cells serves as a marker of microvascular perfusion, while the measurement of the perfused boundary region provides an indirect marker for endothelial glycocalyx barrier dimensions [125]. Research has shown associations between the perfused boundary region and the presence of red blood cells in the microvascular circulation [176]. This method has further revealed that changes in sublingual microvascular blood flow are prevalent in sepsis patients, with the severity of blood flow abnormality correlating to disease severity [177, 178]. However, these techniques have their limitations, and the low reproducibility of three sublingual microcirculation parameters (vascular density, red blood cell filling, and perfused boundary region) estimated by sidestream dark-field imaging remains a topic of discussion. The recently published DAMIS study showed no benefit on survival by including intravital microscopy in clinical decision-making in patients in shock [172, 175].

Improving technology could further help to visualize the endothelial barrier. For instance, the "GlycoCheck™" camera has been shown as a tool to indirectly evaluate the size of the endothelial glycocalyx [179]. Interestingly, Rovas et al. found that the damage to the endothelial glycocalyx seems to be independent of any microcirculatory disruption as gauged by traditional consensus parameters [179]. This implies that patients can have impaired microcirculation without damage to the endothelial glycocalyx, and vice versa.

Treatment considerations

Phases of fluid resuscitation

Importantly, there is no specific treatment for CLS which means tailored therapy needs to focus on nuanced and goal-directed measures to maintain euvolemia and organ perfusion. Fluid administration has to be weighed against potential harm from fluid overload [130, 142], while overzealous fluid resuscitation may further contribute to the degradation of the eGC and subsequently aggravate endothelial injury [108]. While CLS is widely acknowledged in the critical care settings, there is a surprising lack of clinical studies exploring its impact on organ dysfunction and mortality [1]. This may stem from the current absence of accepted diagnostic criteria for CLS. However, associated conditions like an inflammatory state and positive fluid balance—circumstances inevitably related to CLS—correlate with higher mortality rates in the ICU [130]. For example, elevated levels of serum cytokines are commonly observed in non-survivors of critically illness, and a positive fluid balance is acknowledged as an independent predictor of outcomes in patients with sepsis [131, 132].

Fluid management can be complex in ICU settings, demanding a thorough understanding of body fluid homeostasis [133]. Fluid overload, which comprises whole body water, i.e., extra- and intra-vascular fluid, can be detrimental and associated with negative outcomes in patients who are critically ill [134–145]. It has been linked to extended duration of mechanical ventilation [135], increased rate of acute kidney injury [136] and renal replacement therapy [137], longer ICU stays [135], and increased risk of infectious complications [141]. Furthermore, fluid overload can precipitate intra-abdominal hypertension in ICU patients, regardless of the underlying reason for their admission [142]. In all the aforementioned patient categories, fluid overload is consistently associated with increased mortality rates [134, 137, 138, 140–145]. A systematic review by Messmer et al., which encompassed 31 observational and three randomized controlled trials involving a total of 31,076 ICU patients, confirmed a significant correlation between fluid overload and cumulative fluid balance with mortality [146]. Therapeutically, IV fluids may only exert a transient effect on hemodynamics due to their half-life and physiological features to rather liberally cross the vascular barrier [147–149]. It is estimated that less than 5% of infused crystalloid may remain in the vasculature after one hour [150].

To foster the concept of "fluid stewardship" [180], the ROSE model presents a guide for fluid resuscitation in patients with critical illnesses [130]. It revolves around the four D's—the specific drug (type of fluid), dose (volume), duration, and de-escalation (fluid removal) [130, 180]. These four questions aim to guide clinicians in determining the appropriate timing for initiating and discontinuing fluid therapy, as well as when to begin and cease fluid removal. The four indications refer to the purposes of fluid administration: resuscitation, maintenance, replacement, and nutrition [130]. In the ROSE model, fluid management is conceptualized into four distinct phases: Resuscitation, Optimization, Stabilization, and Evacuation. During the Resuscitation phase, fluids are administered to correct hypovolemia. In the Optimization phase, careful titration of fluids is done to ensure adequate organ perfusion. The Stabilization phase then involves a reduction in fluid administration to prevent fluid overload. Finally, in the Evacuation phase, efforts are made to remove excess fluid and return the patient to normovolemia [130]. A possible parallelism to CLS is that during the optimization phase the fluid administration should be guided to maintain/optimize preload despite the developing CLS. During the stabilization phase the intravascular fluid losses due to CLS should be

counterbalanced by a restricted fluid administration, and during the progressive recovery from the CLS permits negative fluid balances during the evacuation phase (see Fig. 3).

Preservation of the endothelial surface layer (ESL)

In this section, the term 'Endothelial Surface Layer (ESL)' will be used to refer to the intricate structure formed by the endothelial glycocalyx (eGC) along with associated plasma proteins. The eGC serves as a luminal mesh that provides endothelial cells with a framework to bind plasma proteins and soluble glycosaminoglycans [181]. While the eGC itself is considered inactive, it becomes physiologically active once it binds with or is immersed in plasma constituents, thereby forming the ESL. It is worth noting that the specific roles and clinical relevance of the eGC as part of the broader ESL are subjects of ongoing research. The ESL is instrumental in maintaining vascular homeostasis, regulating vascular permeability, and acting as a mechanosensor for hemodynamic shear stresses, in addition to displaying antithrombotic and anti-inflammatory characteristics [182]. Plasma proteins, especially albumin, bind within the glycocalyx and aid in stabilizing this layer [183]. Albumin's function is particularly important as it contributes to plasma colloid osmotic pressure (among other, often unmeasured molecules). Moreover, albumin performs a range of roles—from acting as a free radical scavenger and transporting sphingosine-1-phosphate (which has protective effects on the endothelium), to providing immunomodulatory and anti-inflammatory effects [125].

Experimental studies have highlighted the multifunctional nature of albumin, which includes maintaining ESL integrity, partially restoring compromised vascular permeability, exhibiting anti-oxidative properties and anti-inflammatory properties, improving hemodynamics and microcirculation following endotoxemia or hemorrhagic shock, and acting as an effective plasma volume expander [125, 184–190]. Interestingly, beneficial effects appear to be independent of albumin's oncotic properties. Additional research has shown that the choice of fluid for infusion significantly affects the ESL [125, 191]. For instance, in vivo experiments conducted on anesthetized rats subjected to hemorrhagic shock followed by fluid resuscitation, the use of normal saline failed to restore ESL thickness and plasma levels of syndecan-1 [192]. Conversely, albumin was found to stabilize permeability and leukocyte rolling/adhesion, partially restoring ESL thickness and reducing plasma syndecan-1 to baseline levels [125, 192]. Authors have proposed several mechanisms to elucidate the positive influence of albumin on the endothelium [193]. Primarily, albumin might alleviate sepsis-induced damage to the ESL. As reviewed by Aldecoa et al., albumin, due to its amphoteric properties, has the ability to establish strong bonds with the ESL, while its negative

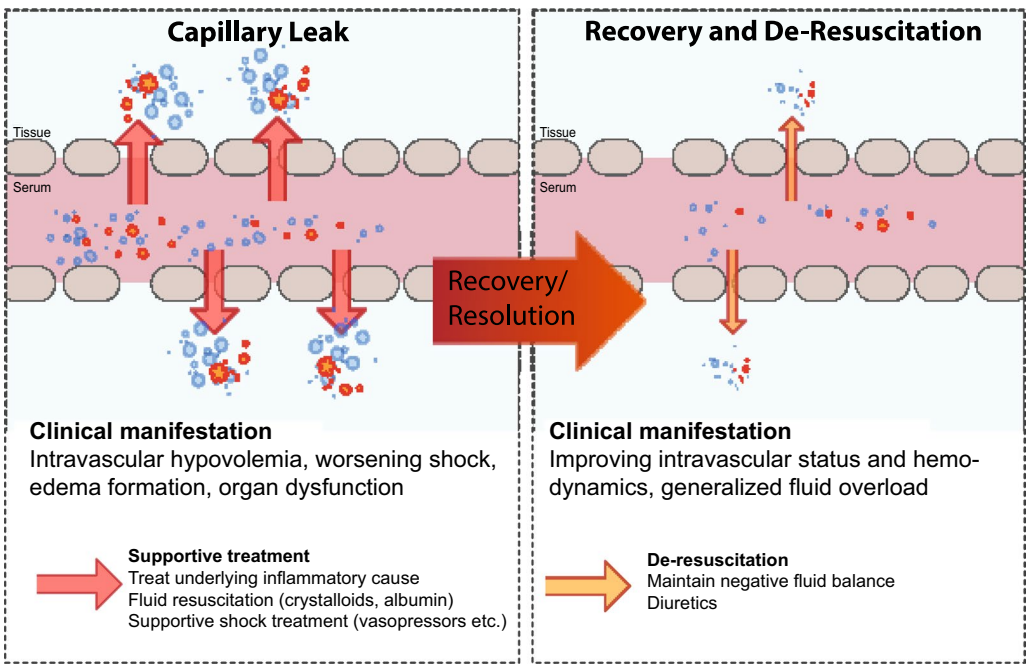


Fig. 3 Phases of capillary leak with increased vascular permeability on the left leading to distinct clinical manifestation and necessitating aggressive treatment strategies, while the recovery phase on the right consists of stabilizing and optimizing the fluid status with de-resuscitation

charge aids in maintaining its parietal electrical barrier [125]. In addition, the antioxidant functions of albumin are well-documented [125]. Albumin's free thiol group, carried by a cysteine residue (Cys-34), assists in neutralizing harmful plasma free radicals, which is highly relevant in the septic environment marked by a high oxidative state. Lastly, albumin's capacity to form complexes with heavy metals provides protection against oxidation via the Fenton reaction [193]. Hariri et al. underscore the mounting evidence, both from experimental models and in the context of critically ill patients, that suggests the protective role of albumin on the endothelium during acute injury [193]. Preservation of the ESL using albumin (and fresh frozen plasma) is intriguing, however clinical studies need to confirm these findings. It is anticipated that the ongoing multicenter ARISS trial will further shed light into the effects of albumin on clinical outcomes [194]. It is crucial to note that commercial albumin solutions are often heated to 60 °C for several hours for inactivation of infectious agents [195]. This heat treatment can lead to protein denaturation and alterations in its negative charge [195], raising the question of the comparability of administered albumin with physiologically circulating albumin synthesized by the liver.

Various clinical studies examine the effects of albumin in the clinical context. Zdolsek et al. have shed light on the impact of exogenous albumin administration on fluid dynamics under various clinical conditions [196]. The primary focus of their study was to evaluate the rate at which infused albumin dissipates from the bloodstream, quantified as the half-life ($T_{1/2}$), under different clinical scenarios. Their research involved intravenously infusing 3 mL/kg of 20% albumin into a varied population that included healthy volunteers, patients after burns, postoperative patients, and patients who underwent surgery with both minor and significant bleeding. The results showed a consistent $T_{1/2}$ across all groups, except for those who experienced surgery with major bleeding. In the latter case, the infused albumin disappeared faster, indicating a greater loss of albumin in situations of significant hemorrhage. Zdolsek and colleagues further compared the effects of 20% and 5% albumin concentrations on plasma volume expansion [197]. The study was designed in a way that the same mass of albumin was administered under both scenarios. Their findings showed that while both concentrations led to plasma volume expansion, the 5% albumin concentration had a slightly higher rate of volume expansion. However, they found that a third of the 5% albumin solution quickly leaked from the plasma, likely due to the higher colloid osmotic pressure of volunteer plasma than that of the albumin solution. By the 6-h mark, about 42–47% of the administered albumin had leaked from the capillaries, regardless of the concentration used.

Further research by Hahn and colleagues investigated the body fluid shifts when 20% albumin is administered intravenously, with a specific focus on postoperative patients [198]. They found that the infused albumin expanded the plasma volume beyond the volume of the infusion itself by moving non-circulating fluid. However, the same mechanism also increased fluid losses from the system. Despite these dynamics, they observed that the plasma albumin level and plasma volume remained stable for about 2 h post-infusion. Therefore, the effectiveness of albumin as an administered fluid may depend on the specific clinical scenario and the administered concentration.

Microvascular and ESL protection prior to surgeries (i.e., before an anticipated inflammatory insult) presents an interesting area of research, as highlighted by Yanase et al. [199]. In their study, they explored the feasibility, efficacy, and safety of potential protective influence of dexamethasone and albumin on the ESL in patients undergoing abdominal surgery. In this trial, patients were randomly assigned to two groups. One group was given intravenous dexamethasone and 20% albumin at the onset of anesthesia, followed by additional albumin with each subsequent crystalloid administration. The control group, conversely, received only crystalloid fluid without dexamethasone leading to differences in the crystalloid, colloid administration. The outcomes were evaluated based on alterations in plasma syndecan-1 and heparan sulfate levels as markers for eGC damage, and inflammatory markers measured at four perioperative timepoints. Although no significant differences were noted in syndecan-1 levels between the two groups, the group that received the dexamethasone-albumin treatment demonstrated lower heparan sulfate and C-reactive protein levels on the first postoperative day, suggesting a potential protective effect on the glycocalyx. This group also experienced fewer postoperative complications [199]. It remains uncertain if this effect is related to the dexamethasone or albumin administration, or the combination thereof.

It has to be noted that the role of albumin administration in critically ill patients has been studied extensively in the past. The ALBIOS trial conducted by Caironi et al. [200] aimed to evaluate the efficacy of albumin administration in patients with severe sepsis. In this multicenter, open-label trial, 1818 patients with severe sepsis were randomized to receive either a 20% albumin and crystalloid solution or a crystalloid solution alone. The albumin group was targeted to maintain a serum albumin concentration of 30 g per liter or more until discharge from the ICU or 28 days after randomization. During the first

7 days, the albumin group demonstrated a higher mean arterial pressure and a lower net fluid balance compared to the crystalloid group. However, no significant difference was observed in the total daily amount of administered fluid between the two groups. The 28-day and 90-day mortality rates did not show significant differences between the two groups, indicating that albumin replacement in addition to crystalloids did not improve survival rates at these timepoints [200]. These findings do not support the hypothesis that albumin administration has survival benefits in severe sepsis, despite previous studies and experimental evidence for its protective role. However, the ALBIOS trial did confirm some physiological benefits of albumin administration. Patients in the albumin group exhibited superior hemodynamic responses, with a higher mean arterial pressure, lower heart rate, and lower net fluid balance in the first 7 days of treatment [200]. The average cardiovascular SOFA subscore was lower in the albumin group, and the time to suspension of inotropic or vasopressor agents was shorter, suggesting a decreased need for vasopressors [200]. Similar to the ALBIOS trial, the ALBICS trial for albumin use in cardiac surgery did not show a benefit on major adverse events at 90 days [201]. Many unanswered questions remain around the role of albumin administration, e.g., its role in effective de-resuscitation and augmenting loop diuretic effects [202] and the comparability of exogenously administered albumin's properties compared to that of circulating albumin. Due to these reasons, no final recommendation can be given for the role of albumin administration for CLS treatment.

Lymphatics in ICU patients

Unlike the cardiovascular system, which ensures bidirectional blood flow, the lymphatic system is specifically designed for unidirectional transit from the extracellular space to the venous system [45]. The lymphatic system plays a pivotal role, actively participating in maintaining tissue fluid equilibrium, aiding in the absorption of lipids from the gastrointestinal tract, and playing an important role in the immune response by transporting antigen-presenting cells and lymphocytes to lymphoid organs [203]. Of note, the lymphatic flow can be increased in health and disease. In the context of critical care, the lymphatic system's potential for increased flow offers interesting avenues for research.

In the critical care setting, physical therapy involving manual lymphatic drainage presents an interesting approach as it has been shown to enhance lymphatic outflow and mobilize fluid [204–206]. Studies have found that manual lymphatic drainage can significantly improve the transportation of various substances within the lymphatic system [204–207]. The findings indicated that manual lymphatic drainage can lead to a modest increase in plasma volume, averaging around 1.5 ± 0.8% [207]. This expansion suggests that lymphatic fluid is being mobilized into the bloodstream. Recent research showed an increase in albumin levels following manual lymphatic drainage [207]. These changes were not solely due to fluid shifts, as albumin concentrations were corrected for changes in plasma volume, and hematocrit remained unaffected by the lymphatic drainage. These observations could imply that the mobilized fluid entering the bloodstream after manual lymphatic drainage therapy possesses a higher albumin content than plasma. The long-term implications of these physiological changes are yet to be fully understood. Nonetheless, the potential role of manual lymphatic drainage in influencing fluid balance and lymphatic outflow could have relevant implications for managing conditions in the ICU.

Experimental approach for endothelial stabilization

Phosphodiesterase (PDE) inhibitors exhibit a diverse range of pharmacological effects, encompassing properties such as anti-inflammatory, antioxidant, vasodilatory, cardiotonic, and anticancer activities, alongside enhancing memory. This expansive superfamily of PDEs is categorized into 11 distinct groups, differentiated by their structural characteristics, cellular localization, gene expression patterns, protein attributes, and a variety of pharmacological properties, influenced by both internal and external regulatory factors. Particularly, phosphodiesterase-4 inhibitors (PDE4-Is, e.g., rolipram and roflumilast) have been explored as potential treatment options stabilizing endothelial interaction during systemic inflammation and sepsis [208, 209]. The proposed mechanism is thought to involve the control of the cAMP/Rac1-signaling pathway, which is integral to the stability of intercellular junctions [208, 210–212]. The intracellular second messenger cyclic adenosine monophosphate (cAMP) decreases in endothelial cells under inflammatory conditions, associated with the breakdown of endothelial barrier properties in vitro [210]. Experimental studies further suggest that administration of PDE4-Is which increases endothelium-specific cAMP holds the potential to maintain cellular adhesion and endothelial barrier properties during acute inflammation. Schick et al. showed in a rodent model that the application of rolipram or roflumilast effectively attenuated capillary leakage and improved microcirculatory flow by preventing the inflammation-induced loss of endothelial cAMP [208]. Wollborn et al. further confirmed the effects of PDE4-Is in extracorporeal circulation-induced capillary leak [209]. Various other pathways remain under investigation to evaluate means to stabilize vascular endothelium [39].

In addition to PDE4-Is, other PDE-Is also show potential in endothelial stabilization. The PDE1 family, known for its vasodilatory effects and reduced activity in platelet aggregation, may influence endothelial stability by modifying vascular tone and cellular cAMP levels, crucial factors in maintaining endothelial barrier integrity [213–215]. Experimental studies suggest that PDE1 inhibitors, by modulating cGMP and cAMP pathways, could potentially reinforce endothelial cell adhesion and barrier properties, similar to the effects observed with PDE4-Is [216–218]. PDE2-Is, through their unique mechanism of cGMP-mediated cAMP regulation, may also contribute to endothelial stability. By enhancing intercellular communication and barrier function, they could offer a novel approach to managing endothelial disruption in conditions such as pulmonary hypertension and heart failure [219–221]. Furthermore, PDE3-Is, while primarily recognized for their cardiac effects, could indirectly influence endothelial function. Given their role in modulating intracellular cAMP levels, they might impact endothelial cell junction stability and barrier properties, particularly under stress conditions such as sepsis or systemic inflammation [222–224]. Among the most promising for endothelial stabilization are PDE5-Is like sildenafil and tadalafil. These agents have shown effectiveness in improving hemodynamics and endothelial function in heart failure and pulmonary arterial hypertension [225–227]. Their mechanism, which involves modulating cGMP-dependent signaling, makes them particularly relevant for maintaining endothelial barrier integrity. While primarily associated with visual functions, the role of PDE6 in other cellular processes remains under-investigated in the context of endothelial stabilization [228], PDE7-Is are present in immune cells and cardiac myocytes and might influence endothelial function indirectly through immunomodulatory pathways [229, 230]. Both PDE8 and PDE9 are involved in cAMP and cGMP signaling, respectively. While their direct role in endothelial stabilization is not as prominent, they may offer insights into cardiovascular functions and pathologies [231–233]. PDE10 and PDE11 are primarily explored for neurological and psychiatric disorders, and tumor development. Their role in endothelial stabilization is less defined [234, 235].

Recent insights have highlighted the pivotal role of vasodilators, particularly prostaglandins, in regulating endothelial capillary permeability. Prostaglandins, notably prostaglandin E2, play a significant role in this regard. Activation of the prostaglandin E2 receptor signal, which induces vasodilation, could be targeted to enhance endothelial barrier function and counteract capillary leak syndrome [236]. Experimental strategies might involve modulating these pathways to optimize vascular tone and permeability. Endothelium-derived vasodilators, including NO, prostacyclin, and endothelium-derived hyperpolarizing factors, play a central role in maintaining vascular tone. NO, synthesized by endothelial nitric oxide synthase, is instrumental in regulating vascular tone and endothelial function [237–239]. For example, strategies that enhance endothelial nitric oxide synthase activity or NO bioavailability could effectively stabilize endothelial function. This might include gene therapy to upregulate endothelial nitric oxide synthase expression, pharmacological agents to increase NO production, or novel compounds to mimic NO's vasodilatory effects [236]. Additionally, addressing endothelial hyperpolarization through endothelium-derived hyperpolarizing factors could offer a novel experimental avenue. This might involve manipulating calcium-activated potassium channels or exploring the roles of gap junctions and epoxyeicosatrienoic acids in endothelial cell signaling [240, 241]. Prostacyclin, generated by cyclooxygenase in endothelial cells, activates adenylate cyclase, leading to vascular smooth muscle relaxation [242]. Its role in vasorelaxation suggests potential therapeutic applications in managing endothelial dysfunction. Modulating prostacyclin levels or mimicking its action through pharmacological agents could be an experimental approach to stabilize endothelial cells and maintain vascular homeostasis [236].

Recently, therapeutic plasma exchange has been used in clinical trials to modulate the injurious endothelial activation. The rationale behind this combines two aspects in one procedure: the removal of injurious circulating factors (e.g., Ang-2, heparanase-1) and the replacement of protective factors that have been consumed by the disease process (e.g., heparanase-2 or Ang-1) [243]. This concept has been demonstrated both by quantifying these factors before and after and by ex vivo stimulation of endothelial cells with plasma from these patients [95, 244, 245].

Conclusion

This review elucidates the multifaceted nature of CLS, underscoring the importance of recognizing its diverse triggers, including systemic inflammation and endothelial barrier breakdown. While current diagnostic methods, such as bioelectrical impedance analysis and serum markers, provide insights, their limitations highlight the need for more precise and universally accepted diagnostic criteria. Treatment strategies, primarily focusing on fluid management and endothelial stabilization, have shown potential, yet they lack specificity and efficacy for CLS. Innovative approaches, like the exploitation of the angiopoietin–Tie2 signaling axis, preservation of the endothelial surface layer, and experimental therapies like phosphodiesterase inhibitors, offer promising directions.

Future research should aim to develop a consensus on CLS definition, establish reliable diagnostic benchmarks, and explore these novel therapeutic strategies to enhance patient outcomes in critical care settings.

Take-home message

CLS presents a diagnostic and therapeutic challenge in critical care due to its complex pathophysiology and the absence of standardized diagnostic criteria. According to the authors of this review, prioritizing research to refine diagnostic tools and explore novel treatments, including endothelial stabilization strategies and experimental pharmacological interventions, is crucial for improving patient management and outcomes in CLS.

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